Office Action Summary	Application No.	Applicant(s)	
	09/703,350	MEHRABAN ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56 and 69-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56 and 69-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/27/2007*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *10/3/2007* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Amendments and Arguments

The Amendment filed on 11/27/2007 in response to the previous Non-Final Office Action (6/28/2007) is acknowledged and has been entered.

Claims 56 and 69-79 are currently pending and under consideration as drawn to a method of inhibiting angiogenesis in a tumor comprising administering to the tumor an antibody to an amino acid sequence of SEQ ID NO: 76.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 11/27/2007 are/is considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed.

Rejection Maintained and Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56 and 69-79 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention stated as the following:

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of inhibiting angiogenesis in a tumor comprising administering to the tumor an effective amount of an antibody or antigen binding fragment thereof that specifically binds and neutralizes a polypeptide comprising SEQ ID NO:76 or binds to an immunogenic

fragment of SEQ ID NO:76. Although applicant has amended claims from originally presented "*inhibiting angiogenesis in a mammal comprising administering to the mammal an antibody*" to currently presented "*inhibiting angiogenesis in a tumor comprising administering to the tumor an antibody*", the Office is examining the claims as originally presented invention as in vivo method of inhibiting angiogenesis in a tumor because original claimed term "administering to the mammal" is drawn to an in vivo method.

The specification teaches that protein of SEQ ID NO:76 is a secreted glycoprotein referred to as a stanniocalcin precursor (page 25). The specification proposes "neutralizing antibodies to stanniocalcin may be useful as therapeutic molecules because they bind to stanniocalcin and thereby remove it from the immediate cellular environment". Thus, the specification appears to broadly claim that the claimed antibodies would predictably provide a therapeutic benefit to humans in need of reducing angiogenesis. For example, the specification teaches that angiogenesis is an important component of a variety of diseases and disorders including tumor growth and metastasis, rheumatoid arthritis, psoriasis, diabetic retinopathy, neovascular glaucoma, etc. (page 12). Thus, the claims broadly encompass methods of treating cancer by administering an antibody that binds to SEQ ID NO:76. However, the specification lacks critical guidance and objective evidence to predictably enable those of skill in the art to practice the invention with success. For example, there is no evidence that inhibition of stanniocalcin activity or removal of the secreted glycoprotein of SEQ ID NO:76 results in the inhibition of angiogenesis with concomitant reduction of tumor cell growth in a mammalian subject. There is no guidance that selective binding of SEQ ID NO:76 with an antibody would predictably reduce tumor cell growth or metastasis in a mammalian subject. The state of the art currently still considers that reducing tumor cell growth and inhibiting disorders associated with angiogenesis is highly unpredictable. For example, Mook et al., (Biochim Biophys Acta, vol 1705:69-89, 2004, abstract) recently comment on treating cancer by inhibition of angiogenesis by inhibiting the function of the proteins, gelatinases regulation of MMP-2 and MMP-9, involved in angiogenesis stating "*MMP-2 and MMP-9 activity regulates bioavailability and activity of growth factors and cytokines, affects the immune response and is involved in angiogenesis. Because of the multifunctionality of gelatinases, it is unpredictable at what stage of cancer development and in which processes gelatinase activity is involved. Therefore, it is concluded that the use of MMP inhibitors to treat cancer should be considered carefully*". Thus, just with regards to inhibiting angiogenesis in general, there is a high standard of accountability recognized by those in this particular area. Based on the very little guidance in the specification, one of skill in the art would not immediately presume that the antibodies would successfully reduce angiogenesis.

Moreover, the pharmaceutical administration of antibodies for the treatment of tumors requires a high degree of guidance as those of skill in the art recognize the unpredictability of treating mammals (including mammals with tumors) via the administration of antibodies. Dillman R. O., (Annals of Internal Medicine, 111:592-603, 1989) summarizes (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). Also, Weiner L. M. (Seminars in Oncology, 26 (4 Suppl 12):41-50, August 1999) provided an overview of monoclonal antibody therapy including some promising activity, however, major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets and insufficient target specificity (see page 43). Again, treatment of cancer in general is at most unpredictable, as underscored by Gura et al., (Science, v 278, 1997, pp.1041-1042, provided in previous office action) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of these underscores the criticality of providing workable examples, which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy. Thus, despite evidence that expression of the stanniocalcin gene is upregulated under endothelial tube-forming conditions and the mRNA is found in cancer tissues, the specification offers no

guidance and or objective evidence that "inhibiting" or neutralizing this activity in a mammal or a tumor would effectively inhibit angiogenesis and treating a tumor.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Previous response to applicant's argument dated 4/11/2007 is maintained for the reason of record as set forth in the Office action dated 6/28/2007.

Response to applicant's argument dated 11/27/2007

The response has been carefully considered but is deemed not to be persuasive to overcome the rejection. Applicant argues four points.

1. At bridging page 4-5, applicant argues:

> That a working example is not necessary for enabling one skilled in the art to practice the claimed invention and a substantial amount of experimentation is permissible if the experimentation is routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.
>
> At page 5, applicant argues that the specification teaches the claimed invention as:
>
> "neutralizing antibodies to stanniocalcin are useful as therapeutic molecules because they bind to stanniocalcin and thereby inhibit stanniocalcin activity (page 25)" and "expression of stanniocalcin was unregulated in endothelial cells undergoing tube formation (page 133)".
>
> applicants show that expression of stanniocalcin was upregulated in endothelial cells undergoing tube formation and stanniocalcin is expressed in ductal mammary adenocarcinoma, squamous cell carcinoma, chrondosarcoma, and renal cell carcinoma vasculature. Stanniocalcin is not expressed in normal vessels.

Applicant then provides teachings of the art on that stanniocalcin (STC-1) and its receptor are detected in the breast cancer cells and stanniocalcin is upregulated in an endothelial tube assay (page 6). In response, first applicant presents the same argument about working example as in the remarks filed on 4/11/2007, which has been responded and maintained for the reason of record as set forth in the Office action dated 6/28/2007 as the following:

> "working examples will not by itself render the claimed invention non-enabled. However, instant claimed invention claim a method that is unpredictable method of using an antibody in vivo for treating a tumor by inhibiting angiogenesis. The specification does not give any direction or guideline for one skilled in the art to use the invention to inhibit tumor growth by administering such antibody to the protein of SEQ ID NO: 76. Showing upregulated stanniocalcin in endothelial cells undergoing tube formation and neutralizing antibody is merely an in vitro result and may be just an invitation for further research of using the antibody in vivo. The research does not

guarantee that the skilled in the art can practice the antibody for inhibiting angiogenesis in vivo by administering the antibody for tumor treatment".

Regarding to the teachings of the art, the tubing assay disclosed by Kahn et al., and angiogenic model with collagen gel and fibrin gel disclosed by Gerritsen et al., are also in vitro model for the angiogenesis assay, which would not be the objective evidence for claimed invention and do not provide predictable expectation of success for the claimed invention of in vivo inhibiting angiogenesis by administering an antibody to polypeptides of SEQ ID NO: 76 (stanniocalcin). Again as discussed in the rejection above: *overview of monoclonal antibody therapy including some promising activity, however, major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets and insufficient target specificity… etc.* Applicant has neither shown that claimed method have been experimented and successfully done, nor shown the evidence or direction indicating predictable expectation of success of claimed method, which could allow one skilled in the art to practice it without undue a quantity of experimentations.

2. At page 7, applicant argues the reference cited in the rejection:

Mook discloses in preclinical animal experiments that inhibitors of MMP reduce cancer progression and metastasis. The inhibitors were not as effective in human clinical trials. However, the human trials were performed on patients with advanced stages of cancer and the animal experiments showed that MMP inhibitors are effective but only when they are administered in early stages of tumor development. Nine angiogenic inhibitors were approved by the FDA and in more than 30 other countries to treat cancer. At least 50 other angiogenic inhibitors with varying degrees of antiangiogenic activity are in phase II and phase III clinical trials.

In response, first, as stated by Mook, the fact of the preclinical animal experiment with an inhibitor of MMP not being able to predict or use for treating human patients with advanced cancer has further confirmed the Office's position that undue quantity of experimentations would be necessary for one skilled in the art to practice claimed invention. Second, regarding to angiogenic inhibitors on clinical trial proved by FDA, applicant is reminded that the patent examination process for a patent application is different from the process of clinical trial of or approval of a drug. The two processes can not be enforced together because each follows its own guideline and rules. In addition, each clinically used or trialed drug approved by FDA

would have been supported by a large amount of experimentations. Thus, one antibody for a specific angiogenesis inducing protein being on trial for treating a cancer does not render that the antibodies for other angiogenic proteins are also used for the same purpose without undue experimentations because the nature of the art as stated in the rejection above.

3. At page 7-8, applicant further argues that the references cited by the Office are old references and methods for enhancing antibody tumor penetration and bio-distribution and reducing HAMA response were known at the time of filing of the present application. In response, since applicant only lists the result of the references and ignores the problem stated in the references, and applicant concludes that one skilled in the art would have reasonably expected that antibodies and fragments bind stanniocalcin, which would be useful for inhibiting angiogenesis in a tumor. Some of the references provided in the rejection are the decade old references, however, the problems pointed out in the references have not been solved. One skilled in the art would agree that the antibody or its fragments developed by immunization of the peptides of stanniocalcin would bind to the stanniocalcin protein or its fragment. However, it does not guarantee to neutralize the function of the stanniocalcin protein and used for inhibiting angiogenesis in a tumor in vivo because one skilled in the art clearly know a) antibody binding to its antigenic protein would not be necessary to neutralize the function of the protein and b) tumor angiogenesis is a complicated process in which many factors or proteins are involved, blocking a function of a protein may not inhibit or affect the entirety of the angiogenic process in a tumor, especially in vivo. Therefore, the objective evidence of using the antibody in vivo would be necessary for the Office to evaluate whether the claimed invention is enabled.

4. At page 8-9, applicant further argues:

> The Office Action has failed to provide any evidence that the human endothelial model for tube formation does not correlate to angiogenesis. While Gura generally suggests that xenograft models are not predictive, Gura also confirms that human cell culture models are more reliable. See Gura at page 1042. Gura therefore does not suggest that the human endothelial cell model for tube formation does not correlate to angiogenesis.
> The human endothelial cell model for tube formation is an art recognized model for angiogenesis. Applicants teach that stanniocalcin precursor expression is dramatically enhanced under tube-forming conditions (see, Example 19, page 142 of the specification and page 25, lines 20-26 of

> the specification). In contrast, lower levels of stanniocalcin precursor are expressed under conditions that do not foster tube formation. Applicants contend this data demonstrates a strong correlation between expression of stanniocalcin and tube-formation.

In response, again the reference by Gura states the problem of using the in vitro screened drug for treating a cancer in vivo, which stands the Office's position, that is, the objective evidence would be important for convincing that the one skilled in the art could use the claimed invention without undue experimentation. The Office agrees that human endothelial cell model for tube formation is an art-recognized model for angiogenesis at the time of filing the claimed invention. The specification, example 19, teaches the up expression of stanniocalcin precursor alone with other angiogenesis factors by human umbilical code endothelia (HAVEC) cell cultured on the collagen. Culturing HAVEC on the extracellular matrix proteins including collagen is a routine in vitro method for growing human endothelial cells. Inhibition of expressing one upregulated gene product in such cultured cells does not present, correlate with, or even suggest an in vivo method of inhibition angiogenesis or use for the tumor treatment.

5. At page 9-10, applicant further argues:

> The Office Action is requiring Applicants to establish enablement to a higher degree of certainty than is required. The significant emphasis by the Examiner on the lack of clinical efficacy and alleged inability of the specification to guarantee success in vivo, in effect is requiring clinical data to establish enablement. An enabling disclosure only requires a reasonable correlation to the scope of the claims. Clinical safety and efficacy is not the standard by which patentability is assessed.

In response, the examination of the application is based on the guideline or direction of MPEP. The Office does not change or establish a higher degree of the requirement for the instant application or any other application being examined. The Office stated before and states here again that no clinical efficacy of claimed method is required for determining whether the claimed invention is enabled for this or any other patent application, although it could add to the patentable weight or support the claimed invention. What the Office asked for this application is providing objective evidence, direction/guideline, and/or example to support the claimed method in order to practice claimed invention by one skilled in the art without undue a quantity of experimentations because the nature of the invention, treating tumor with antibody including inhibiting angiogenesis in a tumor, is NOT predictable.

Thus, applicant's arguments have not been found persuasive, and the rejection is maintained for the reasons of record.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure, which has been disclosed and is maintained for the reason of record as stated in the previous Office Action dated 6/28/2007.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,

Examiner
Art Unit 1642

LY
/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643